ERYSIPELOTHRIX RHUSIOPATHIAE. BACTERIOLOGY AND CHEMOTHERAPY[1]

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Erysipelothrix rhusiopathiae, from the Greek *erysipelas*—a disease, *thrix*—a hair or thread, *rhusius*—reddish and *pathus*—a disease, is the causative organism of swine erysipelas and has been assigned to the family *Corynebacteriaceae*, genus *Erysipelothrix*, Bergey (9), the first member of which, *Erysipelothrix muriseptica*, was found by Koch (86) in the blood of mice following the subcutaneous injection of putrefying blood. The organism gives rise to disease in animals, birds and fish and is responsible for the occupational disease erysipeloid in man. The organism is of some historical interest having been described by Pasteur and Dumas (119); and Pasteur and Thuiller (120) used cultures of this organism to demonstrate the method of artificial immunization by means of live attenuated bacteria for the first time. They were able to protect swine against spontaneous infections by injecting cultures of a strain which had been passed through rabbits.

The first accurate observation of *E. rhusiopathiae* however, is due to Loeffler (102) who found a bacillus, similar to Koch's *E. muriseptica* and to the organism of mouse septicemia (103), in the blood vessels of a pig which had died from swine erysipelas. The scientific investigation of the organism commenced with the classical studies of Rosenbach (138). In this comparative study of the organisms, he suggested the names *E. muriseptica*, *E. porci* and *E. erysipeloides* for the mouse, pig and human organisms, on the grounds that they were different, although closely allied to each other.

Rickmann (135), however, dissented and pointed out that the morphological and cultural distinctions accepted by Rosenbach were not sufficiently definite, or indeed constant, to serve as a means of identification and, since all three organisms agglutinated immune sera to the same degree, he concluded that they were identical, the small morphological differences being ascribed to host variation. This conclusion has been endorsed by Kohl (88) who examined 4 strains of *E. rhusiopathiae* and 7 of *E. muriseptica* and concluded that they were identical or extremely closely related. Topley and Wilson (166) include all three organisms under one chapter heading together with *Listerella monocytogenes*, although the chemotherapeutic studies of Porter and Hale (128), for example, indicate that *L. monocytogenes* may still merit a separate classification.

Konst (91) indirectly supports Rickmann's conclusions as he indicates the possibility of two variants of *E. rhusiopathiae*, the highly virulent one prevalent in Europe, and the weakly virulent one prevalent in North America. Although the highly virulent strain, recently observed in the United States (15, 44) and Canada (46) may have been imported from Europe there is no direct evidence

[1] This review is based on a thesis presented to the Victoria University of Manchester in partial fulfilment of the requirements for the Degree of Master of Science, 1948.

of this and the virulent strain probably developed from the weaker one. Konst suggests that Koch's *E. muriseptica* may be considered as an attenuated strain of *E. rhusiopathiae*—endorsed by the facts that, although differing in their virulence to swine, they have identical morphological, serological and immunological characteristics and are equally virulent for small animals (38, 73).

The presence of *E. rhusiopathiae* in outbreaks of polyarthritis in sheep, "joint-ill" in lambs and occasional infections of cattle, horses, turkeys and peacocks has been recorded (8, 53, 121). More recently, Grey (55) has listed some 39 recorded outbreaks of *E. rhusiopathiae* infection of turkeys in the United States during 1934 to 1947, Szabo (163) describes the infection of pheasants by the organism, and Hartsough (63) the isolation of the organism from farm-raised mink. The infection in man, treated in various ways, has also been the subject of reports by a number of observers (6, 10, 37, 68, 75, 80, 111, 115, 141, 146, 159).

Arising out of the researches by Klauder *et al.* (82, 84), the organism may be a fairly common parasite of fish, although conclusive evidence is lacking as Schoop (145), who recorded the isolation of the organism from fish, used a mouse inoculation method and it is uncertain whether the organisms came from the fish or the mice. In this connection, the Odessa epidemics (155), involving some 200 persons handling freshwater fish, are of interest. In discussing the mode of infection Klauder (81) considers that it is due to actual *contact* with animals, fish, shell-fish or animal matter such as hides, pelts or bones (97, 110). According to Bierbaum and Gottron (11), direct transmission from swine to man appears to be uncommon, although the infection has been met with in veterinary students (113). Actual infection of fish and crustaceans has not been demonstrated (171) although circumstantial evidence suggests that the organism may be present in the slimy coating of salt-water fish (90, 164) from which source Schoop (145) isolated the organism. Hettche (67) and Brunner (20), however, fairly easily infected fish experimentally. The contact theory of infection is endorsed by Verge (171) who describes three forms of the disease as (*a*) generalized, (*b*) intestinal and (*c*) cutaneous. The cutaneous form is commonest and is observed in cooks, kitchen workers, butchers and those who handle fish or cheese, (84) sometimes reaching epidemic proportions as in the 247 cases of erysipeloid which occurred among workers sawing and polishing bones for buttons (97) and the Odessa epidemics already mentioned (155).

THE ORGANISM AS A SAPROPHYTE

E. rhusiopathiae is resistant to salting and putrefaction, is known to survive for long periods outside the body (as is shown by the work of Hettche (67) who found that the organism was able to survive for 4 to 5 days in drinking water and 10 to 14 days in sewage), and is capable of growth in the presence of such inhibitors as sodium azide, crystal violet and potassium tellurite (35, 118). The possibility of the organism enjoying a saprophytic existence outside the body in favorable surroundings has, therefore, been suggested by several workers (5, 51, 166). Supporting this argument, Edwards (38) points out *a*, that the natural history of outbreaks suggest an origin in soil infection rather than a spread from

other centres of infection; *b*, the prolonged survival of the organism in certain materials in a state of high virulence; *c*, the discovery of the organism in the alimentary tract of otherwise healthy pigs; *d*, the independent infection of other animals (e.g., sheep (126), mice (175)) with otherwise indistinguishable organisms which are naturally confined in their pathogenic action to the separate species, but which suggests an adaptation to that species from a common saprophytic ancestor.

Arising out of the high resistance of *E. rhusiopathiae* to putrefactive changes, as shown by Losener (104), who found the organisms alive in month-old carcasses of buried animals, infection may also occur through food, or water, contaminated by infected soil (166).

THE CARRIER

Although infection through the skin may be possible, Hutyra and Marek (73) conclude that the natural disease usually arises through intestinal infection; but attempts to transmit the disease by feeding morbid material or cultures usually fails, although the acute natural disease spreads rapidly in pigs during outbreaks, and virulent organisms are excreted in large numbers in both the feces and urine of pigs suffering from the acute disease. Nocard and Leclainche (116), however, state that the best method of transmitting the disease, experimentally, is by feeding with the viscera of an animal which has just succumbed. *E. rhusiopathiae* has also been recovered from the gall-bladders of pigs which had recently suffered from a mild type of the disease (125) and from the tonsils and intestinal mucosa of *apparently* normal swine (125, 165); and Bramm (14) recovered 6 strains of high virulence from the tonsils of 50 pigs. Carriers, therefore, may play an important part in the spread of *E. rhusiopathiae* infection, and the swine louse (*Haematopinus suis*) has been suggested as a vector (156).

Crougue (50) has reported an epizootic in rats due to a bacillus of the swine erysipelas type, and Drake and Hall (35) have suggested that *E. rhusiopathiae* may be more commonly associated with the rat than has previously been recognized. In partial support of this suggestion reference may be made to the isolation of *E. rhusiopathiae* from a rat by Stiles (157),—but his rat was infected and partially disabled by the disease whereas Drake and Hall's rat, a common brown one, appeared to be normal both on capture and on subsequent autopsy. This may provide a possible explanation for the isolation of *E. rhusiopathiae* from various materials and animals where a source of contamination was obscure. Casual infection of both these rats, however, cannot be excluded.

INFECTION IN MAN

Infection by *E. rhusiopathiae* in man has been reviewed recently by Ehrlich (37) and Barber (5). Man is relatively immune but four clinical categories have been enumerated.

1. *Erysipeloid of Rosenbach.* A mild cutaneous form, usually confined to the hands of food handlers and occurring often during May to September. The studies of Rosenbach (138) established its clinical entity and relation to

swine erysipelas. The difficulty of bacteriological confirmation (5) has been attributed to the organism's location in the deep part of the *pars reticularis* of the corium (23, 36). Serum was the usual treatment before the introduction of penicillin and was claimed (111) to be beneficial.

2. *Septicemic form.* Bloodstream infection in man is rare; but two cases in veterinarians, who later died without a bacteriological examination, were reported (59), and Prausnitz (129) records the fatal case of a ten year old child from whose blood *E. rhusiopathiae* was obtained (no post-mortem was performed). Russell and Lamb (141) reported the first bacteriologically and post-mortem proved case in which *E. rhusiopathiae* septicemia led to endocarditis. The case of a butcher who lacerated his thumb with a meat bone and died 6 months later is given by Klauder *et al.* (83).
3. *Infection via the alimentary tract.* Only one case has been given (40), when infection followed ingestion of salt pork, but infection via the alimentary tract may be much more common.
4. *Severe, generalized, cutaneous form.* A case has been described recently (37) where infection arose by direct contact with an infected hog and involved the hands, right arm, face, neck and eyes. Less frequent clinical and anatomical manifestations are reviewed by Ehrlich (37).

INFECTION IN ANIMALS

The pig. The signs and lesions in pigs vary according to virulence but four clinical entities are described (29).

1. *The acute, septicemic form,* in which illness begins after 1 to 5 days of incubation and the mortality is about 80% with deaths in 3 to 4 days.
2. *The subacute, urticarial form, or "diamonds",* is a mild form with the eruption after 2 to 3 days of well-defined quadrilateral or rhombic hemorrhagic patches on the sides, back and buttocks. Death is unusual and recovery occurs in a few days.
3. *The chronic, cardiac form* may follow the more acute forms or arise independently. Warty vegetations usually develop on the mitral valve and death occurs suddenly, or the animals may live for weeks with signs of cardiac insufficiency or pronounced unthriftiness.
4. *The joint or arthritic form* may also follow the more acute forms or arise independently. It is not fatal but seriously interferes with growth and fattening. A fairly high percentage of hogs killed in slaughter houses have arthritis, but preliminary studies failed to find *E. rhusiopathiae* in all such animals and the organisms obtained were not highly pathogenic for mice (92). Gledhill (50) suggests that the acute disease may be due to a toxemia and the chronic form to invasion of the tissues by the organisms.

The mouse. The infection was first described by Koch (86), and Loeffler (203) found *E. rhusiopathiae* to be a natural pathogen for mice. Wayson (175) gives an account of an outbreak in Californian field mice but there was no apparent association with the natural porcine infection. This is in contrast to the general impression (38) that field mice are resistant. With a widespread occurrence of

swine erysipelas in Europe, however, frequent contamination of mice, if susceptible, might have been anticipated.

The lamb and sheep. Infection is usually of the arthritic type (126) but an outbreak in young lambs characterized by hemorrhagic enteritis and enlarged mesenteric glands has been reported (24). Septicemic outbreaks in lambs (61, 93), and adult sheep (133) have also been studied. In cases of polyarthritis in lambs in England (28), *E. rhusiopathiae* was on one occasion found to be lethal to lambs but not to pigs. Similar outbreaks of arthritis in lambs have occurred in the United States (107, 108, 132), Australia (7, 26, 69, 114, 136, 177) and England (61).

Other animals. The organism differs from *L. monocytogenes* in not being pathogenic to guinea pigs (2, 4, 108, 166) but this has been disputed (41, 52, 96). Infection in rats was discussed earlier. In rabbits, *E. rhusiopathiae* is not consistently fatal and gives a monocytosis in non-fatal cases. When rabbits were infected intracutaneously and re-infected, the lesions were more localized and the erythema smaller in area (74). Isolated cases of infection have been reported in kangaroos (167), a dog (21), a horse (121), a wild boar (168), a reindeer (134, 154) and the organism has been isolated from farm raised mink (63).

INFECTION IN BIRDS

The turkey. The first description of a septicemic form was made in 1904 by Jarosch (74a). The first reported outbreak in the United States was by Beaudette and Hudson (8), and Grey (57) has listed 39 recorded outbreaks in 12 states. Grey describes the disease as of sudden onset, the birds become debilitated and sleepy and may die in 48 to 72 hours. Treatment with serum from an infected turkey has been recorded (100), but Grey (57) discourages the use of specific sera as the birds are sick for too long prior to treatment.

Other birds. Infections in ducks have been described (34, 70, 176), (also in wild duck (13)), and a fatal infection with inconsistent therapeutic serum effects has been reported (53). *E. rhusiopathiae* is pathogenic for pigeons (105), and intramuscular inoculation causes death in 3 to 4 days. The persistence of the infection in pigeons treated with antiserum has been described (58). Kubis (94) found that *E rhusiopathiae* was killed in the small intestine following peroral infection. In fowl, infection is of the septicemic type (16, 38) but a chronic wasting condition, with diarrhea, against which serum acted as both a curative and preventive agent, has been described (123). Two cases of infection in pheasants have been reported (163, 172), and single cases have been recorded in the peacock (54), quail (173), woodthrush (198), ring-necked parrakeet (169) and in geese (101). *Erysipelothrix rhusiopathiae* infection in fowl has been discussed recently by Hudson (71) with reference to the epidemiology of the disease.

ECONOMIC IMPORTANCE OF *E. rhusiopathiae*

Swine erysipelas has been a serious continental infection for over a century. The septicemic form, however, was reported in the United States in 1930 (44) and in Canada in 1933 (46), and recent publications have emanated from Jugo-

slavia (31), Bulgaria (25, 47), Australia (3, 62, 130), Dutch East Indies (147), Switzerland (42), Latvia (137), Portugal (105), South Africa (60), India (131), Kenya (124) and Poland (77). The disease exists sporadically in Great Britain's Eastern Counties (38, 51).

All animals, birds and even fish are susceptible but infection occurs mainly in pigs and this is the basis for the organism's economic importance. The mortality of swine in Germany (1898–1924) cost over 10 million marks (27) and the disease, diagnosed in 17 of the United States, is suggested (160) as a major cause of the 4.8% of swine condemned in 1931–1932 after post-mortem inspection for arthritis and other bone diseases. The investigation of swine erysipelas in the United States (150, 151, 152) showed it to be of wide distribution and that the number of hogs slaughtered, due mainly to arthritis, had increased. In a series of autopsies (142) from 1943–1948, 350 out of 1,600 pigs were infected with all the classical types of swine erysipelas; and losses of pigs, prior to marketing in Great Britain during 1939, were estimated (162) to have exceeded 5 million pounds, a figure which excluded the *major* losses due to swine fever and erysipelas.

When *E. rhusiopathiae* infections in animals and birds together with the occupational hazard in man are considered, then contributions to the study of the problem of swine erysipelas become important to a world facing a shrinking food supply in relation to an increasing population and a rising standard of living.

BACTERIOLOGY

Early work. The cultural and biochemical characteristics of *Erysipelothrix rhusiopathiae* have been reviewed by Karlson and Merchant (79). Pasteur and Dumas' original description in 1882 of a slender bacillus from cases of swine erysipelas was followed in 1886 by Loeffler's description of a slender, short, straight or slightly curved rod giving a typical "test-tube brush" gelatine stab-culture. An organism, gram-positive in character, giving a septicemia in mice, was isolated by Moore (112) from a pig, and long filamentous forms were occasionally seen in cultures. A similar organism was found by Theobald Smith (149). It formed tiny, transparent colonies on a solid medium, but gave variable fermentation reactions, although glucose and lactose broths usually became acid. The description from the earlier studies may be summarized (9) as "rod-shaped organisms with a tendency to the formation of long filaments. The filaments may also thicken and show characteristic granules. Non-motile. Gram-positive. Micro-aerophilic. Catalase negative. Grows freely on ordinary media. Acid but no gas from glucose and a few additional carbohydrates. Parasitic on mammals".

In the early work of some thirteen authors, recently reviewed (79, 181, 182), the differential characteristics of *E. rhusiopathiae* are relatively brief and controversial. Only glucose, and possibly fructose, of the monosaccharides and lactose of the disaccharides gave acid. The trisaccharide raffinose, the polysaccharides dextrin, inulin and starch and the glucoside salicin were not fermented while galactose and glycerol gave variable results. The organism produced α-hemolysis on blood agar, a variable H_2S reaction and had no action on milk. It gave no growth on potato medium, a negative indole test and variable nitrate reduction.

The results indicated that little or no agreement existed about the reactions of *E. rhusiopathiae* on differential media.

Later investigations. The results so far have concerned single strains but several workers have examined a series of strains. Marsh (108) reported on 5 strains associated with arthritis in lambs, Deem and Williams (32) gave data on 37 strains obtained from various types of infection, Karlson (78) outlined results on 52 strains, Barber (5) compared 6 strains with 5 strains of *Listerella monocytogenes*, Watts (174) gave results, mainly immunological, on 43 strains, Karlson and Merchant (79) elucidated the cultural and biochemical properties of 60 strains (54 from swine, 4 from turkeys and 2 from arthritic sheep), and Atkinson (2) reported on 33 Australian strains, but emphasized the immunological basis.

The results have been reviewed recently by Woodbine (181) but some points are of interest. The organism can grow under reduced oxygen tension as well as anaerobically (4, 79), a pH of 7.2 to 7.6 being best for maximum growth. Mice and pigeons but not guinea-pigs are susceptible to the organism, the virulence being enhanced by passage through susceptible animals. Conjunctivitis nearly always occurs in infected mice (2, 4, 181, 182) and, for virulent strains, the infecting dose is not affected by mucin (117), but with less virulent strains the infecting dose is reduced by 1/100 to 1/1000 by using alcohol sterilized mucin. Growth of the organism is favored by glucose, blood or serum, and traces of hemolysin are produced (4) which cause the narrow zones of α-hemolysis, although these may be due to hydrogen peroxide formation (161).

The growth requirements of *E. rhusiopathiae* have been compared with those of *L. monocytogenes* (72). One or more amino acids are necessary, and all the strains need riboflavin. *E. rhusiopathiae* also requires small quantities of oleic acid for growth, the inhibitory effects of excessive amounts (87, 127) being nullified by saponin (72, 139).

The reactions of twelve strains of *E. rhusiopathiae* maintained in the Wellcome laboratories (upon 7 of which chemotherapeutic studies had already been carried out (179, 180)) were also investigated. The cultural and fermentation reactions have been discussed in detail (181, 182). Included in the account is the constitution of Petragnani's medium and the interesting fermentation of maltose in the presence of 5% of horse or bovine serum; variable results were obtained with the horse serum (see 165a, 166 p. 367) but all the strains fermented maltose in the presence of the bovine serum.

Immunology. The serological identity of sheep and pig strains of *E. rhusiopathiae* has been recorded (108); and Barber (4) found no antigenic relation between strains of *E. rhusiopathiae* and *L. monocytogenes*. Outbreaks of swine erysipelas may not always be controlled by immune sera. Watts (174), studying 43 strains found 38 to be of one antigenic type and 5 of another. Sera, of low potency, protected mice against lethal doses of an organism from the same group but not against a strain from the other group. On the other hand, Julianelle (76) using 13 strains, considered them to be a single group antigenically. Atkinson (2) showed that her 33 Australian strains were not antigenically homogeneous, but contained one or two different antigens; there was also an intermediate strain

containing both the specific antigens. The strains could be typed by agglutination with specific absorbed sera. Using serological absorption methods, Gledhill (49), classified 20 out of 31 strains into 4 serological types and showed the strains to be qualitatively homogeneous in respect to their antigens, and that serological differences between the groups could arise from differences in the quantitative, or spatial arrangement of these antigens (122). Using the serologically different strains, Gledhill (48, 49) could find no evidence that immune sera, prepared against one strain, would not also protect against other strains and an effective serum was obtainable whether the viable antigen was of high or low virulence. The production and properties of a thermolabile antigen of *E. rhusiopathiae* have been demonstrated (50) by agglutinin-absorption methods and the passive protection of mice against infection. The concentration of *E. rhusiopathiae* antibodies in the γ-globulin from the sera of supposedly normal pigs has been demonstrated in mouse protection tests (22). The 12 strains of *E. rhusiopathiae* examined by Woodbine (181, 182) were all agglutinated by horse antiserum prepared against one of the strains.

Summary. The bacteriology of *E. rhusiopathiae* may be conveniently summarized under three headings.

1. *Positive reactions.* The organisms occur as short, slender, straight or slightly curved rods, singly or in chains, with a tendency to filamentation. *E. rhusiopathiae* is gram-positive and gelatine or agar, stab or shake, cultures indicate its micro-aerophilic character with a tendency to form a "test-tube brush" appearance. Agar slant cultures, however, show a scanty, low, flat, translucent growth, but cultures on blood-agar give low convex colonies with a narrow greenish zone of α-hemolysis on incubation for 48 hours at 37 C. The organism gives a confluent, raised growth on Loewenstein's egg medium and produces in nutrient broth an even turbidity which is even richer in the presence of one per cent glucose. *E. rhusiopathiae* is usually positive for hydrogen sulphide production. One per cent fructose in peptone water with 5 per cent horse serum gives an acid reaction on incubation with the organism, and there is a tendency for positive reactions with glucose, galactose and lactose under similar conditions. Maltose gives an acid reaction when 5 per cent bovine serum is added to 1 per cent maltose peptone water and incubated with *E. rhusiopathiae*. The organism is pathogenic to mice, causing conjunctivitis and diarrhea, with death in 3 to 5 days. *E. rhusiopathiae* is agglutinated by antiserum prepared against any one strain.
2. *Negative reactions.* Peptone water supports little or no growth when incubated with *E. rhusiopathiae* and no growth occurs in litmus milk. The organism gives negative acetylmethyl carbinol, methyl red, indole and ammonia reactions. Peptone water containing 1 per cent of arabinose, rhamnose, maltose, sucrose, trehalose, raffinose, dextrin, inulin, glycogen, starch, salicin, aesculin, mannitol, dulcitol, or sorbitol gives neither acid nor gas when incubated with *E. rhusiopathiae*. Peptone water containing 5 per cent horse serum and 1 per cent of sucrose, trehalose, raffinose, glycogen, inulin,

salicin, aesculin, dulcitol, mannitol, adonitol or inositol still gives neither acid nor gas when incubated with the organism.

3. *Intermediate, or facultative, reactions.* *E. rhusiopathiae* may give a positive or negative methylene blue test, and the reduction of nitrates may or may not proceed. Inconsistent results follow when the organism is incubated with peptone water containing 1 per cent of glucose, mannose, galactose, fructose, xylose or lactose. Doubtful results are obtained on incubation with peptone water containing 5 per cent horse serum and one per cent of mannose, xylose, maltose, starch or sorbitol.

CHEMOTHERAPY

Historically, the chemotherapy of *E. rhusiopathiae* infections, (181), follows the development of modern chemotherapy as the ubiquity of the organism and the infections it causes in man, birds and animals led to the investigation of new therapeutic agents as soon as they were discovered. The administration of antiserum was the standard practice and is still the method of choice in animal practice owing to the present inadequacy of chemotherapeutic agents; although their use has been aided by the known adverse effects of serum. The reliability of commercially produced vaccines has been examined by Blore *et al.* (12). They found that viability and virulence, over a 6 year period, revealed considerable variation in product acceptability at the expiration date.

Arsenicals. The chemotherapeutic activity of two arsenobenzene derivatives was found to be equal to serum (89). Stovarsol (3-acetylamino-4-hydroxyphenylarsonic acid) has been used successfully for swine erysipelas infection in man by Berthellin and Moulin (10); and Nicol and Mercier (115) also found it of value when used with antiserum.

Sulfonamides. Following the introduction of "prontosil" and *p*-aminobenzenesulfonamide, they and their derivatives were soon essayed in the treatment of *E. rhusiopathiae* infections. Porter and Hale (128), for example, found that sulfanilamide or sulfapyridine, given intraperitoneally, did not protect infected mice, but Schoch and Shelmire (144) successfully treated erysipeloid with sulfanilamide and Kulchar and Rosenberg (95) found sulfathiazole was curative in cases of erysipeloid. Rosler (140) found sulfapyridine and sulfathiazole to inhibit *E. rhusiopathiae* in broth or on plates but in lethal infections in mice, sulfapyridine was the more effective. In deliberately infected swine, however, both sulfonamides failed to protect although the pyrexia appeared to be reduced. In lethal infections in mice sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine (85) had little protective action but concurrent administration of immune serum enhanced their therapeutic effect to a slight extent. In man, sulfathiazole had no protective effect against the septicemic form (83). Sulfathiazole, sulfapyridine, sulfamezathine, and N′-3,4-dimethylbenzoylsulfanilamide had no effect on *E. rhusiopathiae* infection in mice (see 181). King (80) found that sulfathiazole retarded healing in cases of erysipeloid; and the ineffectiveness of sulfathiazole, sulfanilylguanidine, 3-sulfanilamidobenzamide (178) sulphetrone (19) and sulfanilamidobenzamide and phthalylsulfathiazole *in vivo* has been demonstrated

(179, 180, 181). Slavin and MacCay (148) also found sulfathiazole, sulfadiazine, sulfamezathine and sulfapyridine to be ineffective against infections in mice. All the strains of *E. rhusiopathiae* examined were resistant to those sulfonamides owing their mode of action to reversal of *p*-aminobenzoic acid and susceptible, *in vitro*, to benzylamine-4-sulphonamide, which acts by a different antibacterial mechanism, but has no systemic activity (39, 45). It may be deduced that the organism does not utilize *p*-aminobenzoic acid as a growth factor. The results justify the conclusion that the range of sulfonamides examined so far is ineffective in the chemotherapy of such infections.

Antibiotics. Penicillin has been found to be antibacterial *in vitro* to the allied organism *Listerella monocytogenes* (43); and Heilman and Herrell (65, 66) reported that the antibiotic was antibacterial to *E. rhusiopathiae in vitro* and exceedingly effective against infections in mice. In 1945, penicillins G and X were found to be antibacterial *in vitro* (97). Extremely large peroral doses of penicillin protected mice infected with *E. rhusiopathiae* (64), and repeated doses were effective in infected pigeons (170). Intramuscular penicillin was successfully used by Hodgson (68) for 2 cases of erysipeloid (see also 6, 75). Stiles (158) used penicillin as an adjunct to antiserum therapy for *E. rhusiopathiae* infection in turkeys but with inconclusive results. Yet Grey (55, 56) found penicillin to be active *in vitro* and *in vivo* in infections of mice and in treating infected turkeys with relatively low doses (56). A case of chronic erysipeloid in man was cured by penicillin (159), and Whitten *et al.* (177) have tried penicillin in cases of erysipeloid of sheep. All the 12 strains of *E. rhusiopathiae* examined *in vitro* by Woodbine (179, 180, 181) were susceptible to penicillin and results of daily readings showed that it has a higher degree of "inhibiting-concentration maintenance" than either streptomycin or benzylamine-4-sulfonamide (181). The low degree of protection obtained with penicillin *in vivo* (179, 181) is less than that expected from the *in vitro* results, particularly in view of the observed relationship between *in vitro* and *in vivo* results obtained with other gram-positive pathogens. This degree of *in vitro* bacteriostasis should not require the large doses of penicillin which appear to be necessary to show even a temporary protection in mice. A partial explanation for this anomaly may lie in the possible development of mutants (33) or to the production of the neutralizable toxin as suggested by Gledhill (51). The prognosis in man is good (5) as there is a tendency for spontaneous resolution in cases of erysipeloid (85). The relatively low doses used by Grey (56) indicates that there is some natural resistance to infection in turkeys, as the strains used are not significantly different in penicillin sensitivity to those maintained elsewhere (181). In a comparison of penicillin and antiserum treatment of swine erysipelas in turkeys, Brown *et al.* (17) found penicillin to be the more effective agent.

Under these circumstances the advent of streptomycin, with its widely claimed activity against organisms insusceptible to penicillin, was of considerable interest. Schatz and Waksman (143) reported that streptomycin was effective *in vitro* against *E. rhusiopathiae*. The effectiveness of streptomycin *in vitro* and *in vivo* against infections in mice, was reported by Woodbine (180) and in infected tur-

keys was described by Grey (57). Mixtures of streptomycin with benzylamine-4-sulfonamide or penicillin showed no evidence of any synergic action *in vitro*, and penicillin was about 100 times as effective as streptomycin, weight for weight (180, 181). The antibacterial activity of stryptomycin against *E. rhusiopathiae* showed inhibition of growth at higher concentrations than penicillin and larger doses were used in chemotherapeutic comparisons (180, 181). The results showed that streptomycin was less effective than penicillin but that there was a synergic effect when the two antibiotics were given together in equal doses. The results in mice indicated that infections of *E. rhusiopathiae* in swine would not prove readily amenable to chemotherapy with either streptomycin, penicillin or penicillin plus streptomycin simultaneously, and that antiserum still remained the method of treatment.

The introduction of "aerosporin" (now, polymyxin B) (1,18) was followed by an assessment of its potential value against *E. rhusiopathiae*. The related antibiotic "polymyxin" (now, polymyxin D (153)) is inactive *in vitro*. Results of comparisons with penicillin, streptomycin and benzylamine-4-sulfonamide *in vitro*, showed that polymyxin B was inactive against *E. rhusiopathiae* (181). The assessment of polymyxin B *in vivo* provided an opportunity of assessing the activity of penicillin and streptomycin against four United States strains of *E. rhusiopathiae* (used by Grey (55,56,57)) and the strain isolated in Argentina (181,182). The results showed (181) that polymyxin B is inactive *in vivo* and that penicillin and streptomycin are as active against the American as against the indigenous strains of *E. rhusiopathiae*.

Summary. The chemotherapy of infections by *E. rhusiopathiae* may be summarized by the following statements.

All the strains of *E. rhusiopathiae* examined are resistant *in vitro* to those sulfonamides owing their activity to reversal of *p*-aminobenzoic acid, and are not amenable to chemotherapy with these compounds. All strains of *E. rhusiopathiae* are sensitive to benzylamine-4-sulfonamide, penicillin and streptomycin *in vitro*, and penicillin is more active, weight for weight, than streptomycin. Penicillin and streptomycin, in high doses, protect mice against infections by *E. rhusiopathiae* and a synergic action is obtained with penicillin and streptomycin simultaneously. The experimental results indicate that *E. rhusiopathiae* infection in swine is not yet amenable to chemotherapy and that antiserum still retains its accepted place. The antibiotics, however, appear acceptable for treating infections by *E. rhusiopathiae* in man and in birds, particularly turkeys.

The author wishes to express his thanks to Dr. W. E. Herrell for his support in preparing the review, to Dr. A. W. Gledhill for his kindly criticism and help, to Dr. G. Brownlee for the initiation into and encouragement in research, to his friends and late colleagues, especially Mr. M. W. Cheeseman, Mr. S. Bowden and Mr. A. Seaman, of the Wellcome Research Laboratories, for their courtesy, help, advice and encouragement during his stay there, and to the Wellcome Foundation Ltd., for their facilities and support.

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